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Dated 28 May 2003

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P01/7700 0.00-0221579.6

THE PATENT OFFICE
17 SEP 2002
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# Request for grant of a patent

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The Patent Office

Cardiff Road
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1. Your reference — PC25214

2. Patent application number *(The Patent Office will fill in this part)* — 0221579.6 — 17 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

PFIZER LIMITED
Ramsgate Road,
Sandwich,
Kent, CT13 9NJ

6892673001

Patents ADP number *(if you know it)*

United Kingdom

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — COMBINATIONS OF ATORVASTATIN AND $\alpha_1$ ADRENERGIC RECEPTOR ANTAGONISTS

5. Name of your agent *(if you have one)*

Dr. S. Cosway

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

UK Patent Department
Ramsgate Road,
Sandwich, Kent,
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United Kingdom

1271001

Patents ADP number *(if you know it)*

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
|---|---|---|

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
|---|---|

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
*c) any named applicant is a corporate body.*
*See note (d))*

# Combinations of atorvastatin and $\alpha_1$ adrenergic receptor antagonists

This invention relates to combinations of atorvastatin and $\alpha_1$ adrenergic receptor antagonists, the use of such combinations in the treatment of benign prostatic hyperplasia (BPH), methods of treating BPH using such combinations and medicaments containing such combinations.

BPH is a chronically progressive disease that can lead to complications such as acute urinary retention, recurrent urinary tract infections, bladder stones and renal dysfunction. The prevalence and average severity of lower urinary tract symptoms (LUTS) associated with BPH in men increases with age.

BPH leads to an increase in prostate volume, creating urethral and bladder outflow obstruction as well as secondary changes in bladder function. The effects of this are manifested by both storage (irritative) and voiding (obstructive) symptoms, giving rise to nocturia, urinary urgency and poor urinary flow.

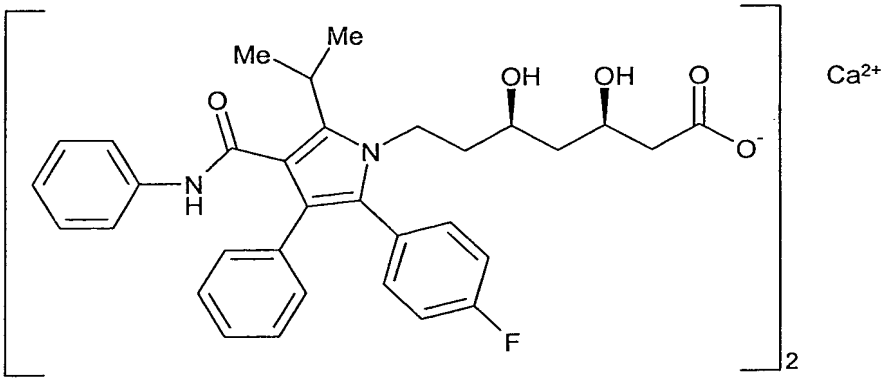
In patients with BPH, blockade of sympathetic (adrenergic) nerve innervations of the prostate reduces intra-urethral pressure by about 50% (J. Urol., **1982**, *128*, 836), alleviating the symptoms of outflow obstruction. In particular, adrenergic receptors of the $\alpha_1$ subtype predominate in the prostate and lower urinary tract and $\alpha_1$ adrenoceptor-specific antagonists have been identified which preferentially relax prostatic smooth muscle compared with cardiovascular smooth muscle. Clinical trials have confirmed this hypothesis and several $\alpha_1$ antagonists such as tamsulosin, terazosin, alfuzosin and doxazosin are now marketed for the treatment of BPH.

Many reviews of $\alpha_1$ adrenoceptor antagonists are available, for example see *Prostate Cancer Prostatic Dis.* **2000**, *3*, 76-83; *Annu. Rep. Med. Chem.* **2000**, *35*, 221-230; *Expert Opin. Invest. Drugs,* **1999**, *8*, 2073-2094; *Prostate Cancer*

*Prostatic Dis.*, **1999**, *2*, 110-119; *J. Med. Chem.*, **1997**, *40*, 1293; *Pharm. Res.*, **1996**, *33*, 145.

While, the introduction of pharmacological therapies has heralded some improvement in the impact of the symptoms and the need for surgical intervention for BPH, the overall effects are moderate and the needs of patients and physicians are still largely unmet. Also there is no evidence that the currently available pharmacological therapies are effective at controlling either the bladder hypertrophy, detrusor instability, or prostate/bladder fibrosis associated with BPH.

Atorvastatin calcium, disclosed in U.S. Patent No. 5,273,995, is currently sold as Lipitor®, and is [R-(R*, R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt, represented by formula I below:




It is known to be a potent inhibitor of HMG-CoA reductase.

Italian Patent Application No. 048658 describes the use of HMG-CoA reductase inhibitors for the treatment of BPH. US2002/0004521 describes the use of atorvastatin for the treatment of BPH. Combinations of 5α-reductase inhibitors with α-adrenergic receptor antagonists are described for use in the treatment of BPH in US Patent No. 5,753,641. WO 99/11260 concerns the combination of atorvastatin with an antihypertensive agent, which may comprise an α-

adrenergic receptor antagonist. Such combinations are useful in the treatment of angina pectoris, atherosclerosis, combined hypertension and hyperlipidemia and for the treatment of subjects presenting with symptoms of cardiac risk.

This invention provides the use of a combination of (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) an $\alpha_1$-adrenergic receptor antagonist or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of BPH. Pharmaceutically acceptable derivatives include pharmaceutically acceptable salts and pharmaceutically acceptable solvates.

Further, it provides the use of a combination of (A) and (B) for the treatment of BPH in order to improve lower urinary tract symptoms and urinary flow rates, limit progression of the disease and reverse the pathological changes in the bladder and prostate associated with the disease, thus reducing the incidence of urinary retention and the requirement for surgery.

The combinations of the invention may have the advantage that, due to a synergistic interaction between the active ingredients, they are more potent, have a longer duration of action, more effectively reduce disease progression and, therefore, the requirement for surgical intervention, have a broader range of activity, are more stable, have fewer side effects or are more selective (in particular they may have beneficial effects in BPH without causing undesirable cardiovascular effects) or have other more useful properties than the prior art.

In one embodiment, there is provided the use of a combination of (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) an $\alpha_1$-adrenergic receptor antagonist or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of BPH. $\alpha_1$-Adrenergic receptor antagonists useful for (B) include, but are not limited to, terazosin (US Patent No. 4,026,894), doxazosin (US Patent No. 4,188,390), prazosin (US Patent No. 3,511,836), bunazosin (US

Patent No. 3,920,636), alfuzosin (US Patent No. 4,315,007), naftopidil (US Patent No. 3,997,666), tamsulosin (US Patent No. 4,703,063), silodosin (US Patent No. 5,387,603); or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline (International Patent Application Publication No. WO 98/30560, example 19); and pharmaceutically acceptable derivatives thereof. A preferred α-adrenergic receptor antagonist is 4-Amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline and pharmaceutically acceptable derivatives thereof. The mesylate salt is of particular interest (see WO 01/64672).

A further embodiment comprises a pharmaceutical composition comprising (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable derivative thereof.

In a further embodiment there is provided a medicament containing, separately or together, (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable derivative thereof, for simultaneous, sequential or separate administration in the treatment of BPH.

In a further embodiment there is provided a pharmaceutical composition comprising a mixture of effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined, optionally together with a pharmaceutically acceptable carrier.

In the pharmaceutical compositions of the present invention, (A) is present in an amount ranging from 10 mg to 80 mg per dose, and (B) is present in an amount ranging from 0.1 mg to 20 mg per dose. The physician in any event will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of

course, be individual instances where higher or lower dosage ranges are merited and such are within the scope of this invention.

The pharmaceutical compositions of the present invention can be administered alone but will generally be administered in a mixture with a suitable pharmaceutical excipient, diluent or carried selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the pharmaceutical compositions can be administered orally, buccally or sublingually in the form of tablets, capsules, multi-particulates, gels, films, ovules, elixirs, solutions or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. The pharmaceutical compositions may also be administered as fast-dispersing or fast-dissolving dosage forms or in the form of a high energy dispersion or as coated particles. Suitable formulations of the pharmaceutical compositions may be in coated or uncoated form.

Solid pharmaceutical compositions, for example tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

The pharmaceutical compositions may also be administered in the form of a suppository for rectal administration. These compositions can be prepared by mixing the drug with a suitable non-irritating excipients which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

The combination of this invention may also be administered in a controlled-release dosage formulation such as a slow release or a fast release formulation. Such controlled release formulations of the combination of this invention may be prepared according to methods well known to those skilled in the art.

Pharmaceutical compositions according to the invention may contain 0.1%-95% of the compounds of this invention, preferably 1%-70%.

Still further provided by the present invention is a method of treating BPH comprising administering to a subject in need of such treatment amounts of (A) as hereinbefore described and (B) as hereinbefore described which are together effective.

Yet further, there is provided by the present invention a pharmaceutical product containing (A) and (B) as hereinbefore defined, as a combined preparation for simultaneous, separate or sequential use in treating BPH.

"Effective amounts" as used herein is an amount of (A) and (B) that will elicit the biological or medical response being sought. The daily dose of (A) and (B) employed in the method of treatment is similar to the doses described for use in the pharmaceutical compositions hereinbefore described. In the method of treatment according to the present invention (A) and (B) can be administered together combined in a single dosage form, or they can be administered separately, essentially concurrently, each in its own dosage form but as part of the same therapeutic treatment program, and it is envisaged that (A) and (B) may be separately administered, at different times and by different routes.

The utility of the combination of the present invention as medical agents in the treatment of BPH is demonstrated by the activity of the combination in the protocol described below:

Efficacy of atorvastatin and doxazosin on benign prostate hyperplasia (BPH) in the spontaneous hypertensive rat (SHR).

This study is designed to investigate the effects of atorvastatin at 1, 10 and 30 mg/kg, and concomitant treatment with 0.1 mg/kg of doxazosin on bladder function (as assessed by cystometry i.e. the flow of urine through the bladder/urethra) and gross prostate morphology (prostate weight, stromal/epithelial volume) of spontaneous hypertensive rats (SHR).
SHR's have increased prostate size (increased stromal and epithelial growth), and bladder hyperactivity relative to their normotensive Wistar-Kyoto (WKY) counterparts. These changes in bladder function and prostate morphology reflect those observed in men with BPH. All tissue samples collected (prostates) were examined for size and gross cellular morphology (stromal content and epithelial thickness) as an indication of BPH.

The animals were group housed under 12:12 hour light:dark cycle. They were offered a standard rat diet and water *ad libitum.*

One hundred, 12 week old, spontaneously hypertensive male rats (SHR; Harlan UK) were allocated randomly to 5 treatment groups; (i) placebo (ii) combination at the rate of 1 mg/kg/d po, (iii) combination 10 mg/kg/d po (iv) combination 30 mg/kg/d po or (v) doxazosin 0.1 mg/kg/d. A further control group consisting of 20 normotensive rats Wistar-Kyoto (WKY) was included in the study, these animals received placebo treatment.

The SHR and WKY animals were administered orally their respective treatments for a period of 60 days. Micturition parameters (frequency, volume void and total volume over a 2 hour period) were assessed on a sub-group of animals on days 0, 25 and 50 of the study.

On days 30 and 60 of the experiment, 10 animals from each treatment group were selected randomly to undergo terminal anaesthesia studies to assess the

effects of treatment on bladder/urethral function (cystometry, i.e. urine flow through the bladder/urethra) and prostate size.

Animals were anaesthetised using urethane (1.2 g/kg, i.p.). Depth of anaesthesia was assessed by the stability of blood pressure and heart rate, and by an absence of hind limb withdrawal in response to paw pinch. Supplementary doses of urethane (0.1 g kg-1, i.v.) were given where necessary. The trachea was intubated to maintain a patent airway. The left jugular vein was cannulated for drug administration, and the left common carotid artery was cannulated with a heparinised cannula (20 units/ml heparin in 0.9% w/v saline) for the measurement of arterial blood pressure and for sampling arterial blood for blood gas analysis.

Blood pressure was measured using a pressure transducer (Gould Statham P23Db), and the heart rate (HR) derived electronically on-line from the blood pressure using PoneMah (Linton Pty Ltd UK). Body temperature was monitored with a rectal temperature probe and maintained between 36 – 38°C using a homeothermic blanket system (Harvard, UK).

The animals either spontaneously breathed air or were artificially ventilated, and blood gases were maintained between 90 – 130 mmHg Po2, 40 – 50 mmHg PCo2 and pH 7.3 – 7.4. Adjustments of the supplemented oxygen levels (spontaneously breathing animals) and respiratory pump rate and volume (artificially ventilated animals) were made as necessary to maintain blood gas and pH balance.

The urinary bladder was exposed by a midline abdominal incision. A cut was made in the bladder dome and double lumen cannula (0.52 mm internal and 1.2 mm external diameter) was inserted into the bladder, one of which was connected to a pressure transducer (Gould Statham P23Db) to record intravesical bladder pressure, and the other connected to a syringe pump for the infusion of saline (0.9% w/v) to evoke the micturition reflex. The rate (0.046

ml/min) of infusion of saline into the bladder was chosen to simulate the maximal hourly diuresis rate (Klevmark, 1974).

Following the surgical procedure the animals were allowed to stabilise for c. 30 min. After the stabilisation period, cystometry was performed. Bladder/urethral function and total volume voided were assessed over a 60 minute period.

A microsphere technique was employed to assess the effects of treatment on prostate and bladder blood flow (see Das *et al*, 2002). Briefly, 2 million Nuflow fluorescent red microspheres (IMT; 15 μm diameter suspended in 0.4 mL of 0.9% saline and 0.01% Tween-80) were injected via the carotid catheter. Blood samples were collected prior to, during and following the infusion of microspheres. Five minutes after the infusion the rats were euthanised and the bladder, urethra and prostate collected and blood flow determined. Any change in prostate size alters bladder blood flow and improves bladder function.

Following cystometry, a 2 mL blood sample was collected into heparinised tubes, plasma prepared as soon as possible and stored at –20°C pending analysis for the combination.

Immediately following the termination of the experiment the prostate of the rats was collected, weighed, stored in 10% formalin pending gross morphological examination of the stroma and epithelial thickness.

Differences between treatment groups were examined using ANOVA.

CLAIMS:

1. The use of a combination of (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) an $\alpha_1$-adrenergic receptor antagonist or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of BPH.

2. The use of a combination as defined in claim 1 for the treatment of BPH.

3. The use of a combination of (A) as defined in claim 1 and (B) as defined in claim 1 for the manufacture of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of BPH.

4. The use according to any of claims 1 to 3, wherein (B) is selected from terazosin, doxazosin, prazosin, bunazosin, alfuzosin, naftopidil, tamsulosin, silodosin, 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable derivative thereof.

5. The use according to claim 4, wherein (B) is 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable derivative thereof.

6. A method of treating BPH comprising administering to a subject in need of such treatment amounts of (A) and (B) as defined in claims 1 to 5 which are together effective.

7. A pharmaceutical product containing (A) and (B) as defined in claims 1 to 5, as a combined preparation for simultaneous, separate or sequential use in treating BPH.

8. A pharmaceutical composition comprising (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable derivative thereof.

9. A medicament containing, separately or together, (A) atorvastatin or a pharmaceutically acceptable derivative thereof and (B) 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline or a pharmaceutically acceptable derivative thereof, for simultaneous, sequential or separate administration in the treatment of BPH.

10. A medicament according to claim 9 which is a pharmaceutical composition comprising an effective amount of a combination of (A) and (B), optionally together with a pharmaceutically acceptable carrier.

**Abstract:**

This invention relates to combinations of atorvastatin and $\alpha_1$ adrenergic receptor antagonists, the use of such combinations in the treatment of benign prostatic hyperplasia (BPH), methods of treating BPH using such combinations and medicaments containing such combinations.